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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,946	10/02/2003	Jong Wook Hong	20174C-010310	7287

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EXAMINER	
KIM, YOUNG J	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 08/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/678,946	**Applicant(s)** HONG ET AL.	
	Examiner Young J. Kim	**Art Unit** 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *1-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date *7/26/04 & 11/17/05*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

11/DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group VI, claims 67-75 in the reply filed on July 27, 2006 is acknowledged.

Claims 1-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 27, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

The IDS received on July 26, 2004 and November 17, 2005 are acknowledged.

The signed copies of their PTO/SB/08 are enclosed herewith.

Claim Interpretation

Claims 67 and 69 recite the phrase, "biological entity or the subset of biological entities."

It appears that the phrase should read, "biological element or the subset of biological elements" for claim term consistency.

Correction is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73 and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73 and 75 are indefinite for failing to recite a final process step which agrees back with the preamble. While minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. See *Ex parte Elrich*, 3 USPQ2d, p. 1011 (Bd. Pat App. Int. 1986). For example, Claims 73 and 75 are drawn to a method of obtaining genetic information regarding an individual biological element of a complex environment sample, yet the claims recite a final step amplifying at least a portion of the purified nucleic acid (claim 73) or transforming a cell with said amplified, purified nucleic acid. The claims do not set forth the conditions/state when the method has been completed [i.e., needs to agree with preamble].

Amending claim 73 to incorporate the limitation imposed by claim 74 would overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pethig et al. (Tibtech, 1997, vol. 15, pages 426-432; IDS ref) in view of Lipshutz et al. (U.S. Patent No. 6,043,080, issued March 28, 2000).

Pethig et al. disclose a method of sorting cells from a sample comprising a heterogenous population of cells (Abstract; page 428, 2nd column, bottom paragraph through page 429, 1st column, 2nd paragraph; page 429, 2nd column, 1st paragraph) by use of DEP (dielectrophoresis).

The artisans disclose that because different species of bacteria are known to have large differences in their cell-wall properties which gives them difference in their effective conductivity, by adjusting the medium conductivity, such property can be exploited to selectively separate bacteria from mixtures of difference species (page 429, 1st column, bottom paragraph).

The artisans also explicitly envision the incorporation of this method on a laboratory-on-a-chip device (i.e., microfluidic device) (page 431, 2nd column, 1st paragraph).

The artisans do not explicitly disclose that their method be combined with the lysing of the isolated cells, followed by the purification of the desired nucleic acids, followed by their amplification.

Lipshutz et al. disclose a method of using a microfluidic device which comprises multiple chambers which conduct different types of assays, including sample preparation (column 2, lines 14-32), wherein the chambers include sample preparation chamber (column 4, lines 49-54; column 5, lines 15-20), which explicitly involve extraction of nucleic acids from the cells (column 5, lines 23-27), involving purification of the extracted nucleic acids from other components of the cells (column 5, lines 29-32), followed by the amplification of the nucleic acids (column 6, lines 25-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Pethig et al. with the teachings of Lipshutz et al., thereby arriving at the claimed invention for the following reasons.

The art of microfluidic device which performs many biological reactions on a single chip has been well-established in the art the benefits of which is also widely known as (e.g., time efficient, less sample amount, less sample transition resulting in less contamination, etc.)

Pethig et al. clearly show a method of being able to separate different types of cells from a heterogenous population of cells comprised by a sample by DEP, wherein the artisans clearly express that their method is a "promising tool for the selective manipulation and separation of cells, bacteria and other microorganisms, as well as viruses..." (page 431, 1st column, bottom paragraph).

Coupled with the artisans' explicit teaching which state that the integration of this module into a "lab-on-a-chip device" (page 431, 2nd column, 1st paragraph), one of ordinary skill in the art at the time the invention was made would have been clearly motivated to combine the teachings of Pethig et al. with the teachings of artisans which involve microfluidic device, such as that of Lipshutz et al., so as to arrive at a method of selectively isolating and selecting cells from a heterogeneous population of cells, followed by the isolation of their nucleic acid molecules therein, for the purpose of determining/studying/identifying said nucleic acid molecules from the selectively isolated cells in a time efficient, reagent-efficient manner, with less contamination.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 70, 71, and 73-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burlage (US 2003/0099928, published May 29, 2003, priority September 16, 1999) in view of Pethig et al. (Tibtech, 1997, vol. 15, pages 426-432; IDS ref) and Lipshutz et al. (U.S. Patent No. 6,043,080, issued March 28, 2000).

Burlage discloses a method of separating particular cells from an environmental sample, wherein the method comprises:

a) providing an environmental sample comprising heterogeneous biological elements (section [0040]);

b) physically isolating an individual biological element or a subset of biological elements of the sample (sections [0010]; [0017]; [0035]; and [0065]);

c) lysing the isolated cells to liberate the nucleic acids present herein (section [0069]);

d) purification of the nucleic acids (section [0084]); and

e) amplification of the purified nucleic acid (sections [0069] and [0085]).

With regard to claim 71, the genetic diversity of a Pseudomonas is elucidated by sequence analysis (section [0088]).

With regard to claim 74, the artisan teaches that the genetic information represented by the amplified product is identified by sequencing and comparing against the known sequences (sections [0016]; [0072]; and [0088]).

With regard to claim 75, the artisans teaches that the isolated nucleic acid is cloned and cultured into a culturable microorganism to synthesize the gene product (section [0072]).

Burlage while conducting all of the steps of the claims, does not involve a microfluidic device, and particularly, the physical separation of cells is achieved by in situ hybridization followed by FACS (fluorescence-activated cell sorting; *see* sections [0059]; [0062]; and [0065]).

Pethig et al. disclose a method of sorting cells from a sample comprising a heterogenous population of cells (Abstract; page 428, 2nd column, bottom paragraph through page 429, 1st column, 2nd paragraph; page 429, 2nd column, 1st paragraph) by use of DEP (dielectrophoresis).

The artisans disclose that because different species of bacteria are known to have large differences in their cell-wall properties which gives them difference in their effective conductivity, by adjusting the medium conductivity, such property can be exploited to selectively separate bacteria from mixtures of difference species (page 429, 1st column, bottom paragraph).

The artisans also explicitly envision the incorporation of this method on a laboratory-on-a-chip device (i.e., microfluidic device) (page 431, 2nd column, 1st paragraph).

Lipshutz et al. disclose a method of using a microfluidic device which comprises multiple chambers which conduct different types of assays, including sample preparation (column 2, lines 14-32), wherein the chambers include sample preparation chamber (column 4, lines 49-54; column 5, lines 15-20), which explicitly involve extraction of nucleic acids from the cells (column 5, lines 23-27), involving purification of the extracted nucleic acids from other components of the cells (column 5, lines 29-32), followed by the amplification of the nucleic acids (column 6, lines 25-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Burlage, Pethig et al., and Lipshutz et al., thereby arriving at the claimed invention for the following reasons.

The motivation to analyze unculturable microorganisms from an environmental sample comprising a heterogeneous population of microorganisms is explicitly disclosed by Burlage:

> "Unculturable microorganisms are those microorganisms that cannot be grown in pure cultures by known means. It has been hypothesized that majority of microorganisms are unculturable in any microbial environment, for reasons that are unclear. These unculturable microorganisms represent a vast, untapped resources of DNA and of potential products such as enzymes and other protein products. These microorganisms undoubtedly have undiscovered enzymes that would be useful for environmental, medical, or industrial applications. However, these potential products are currently unavailable because there is no way to obtain pure DNA from such microorganisms. Microorganisms are presently studied at the genetic level by cloning and sequencing their DNA. However, this requires the cultivation of a large number of cells with subsequent extraction of the DNA from the batch. The same approach obviously can not be used for unculturable microorganisms." (sections [0003] and [0004]).

Based on such explicit motivation, one of ordinary skill in the art at the time the invention was made would have recognized the clear need to separate and individually analyze unculturable microorganisms from a sample comprising a heterogeneous population of microorganisms such as an environmental sample.

While Burlage employs techniques such as FACS for cell sorting, followed by subsequent manual operation of DNA extraction, and amplification of the extracted nucleic acids, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a microfluidic device which is well known and recognized in its ability to incorporate many biological assays into a single chip, so as to benefit from its ability to employ less sample/reagents, reduce the chances of contamination; and reduce the time required for the assay.

Pethig et al. clearly show a method of being able to separate different types of cells from a heterogenous population of cells comprised by a sample by DEP, an improvement over the traditional means of cell sorting such as FACS, wherein the artisans clearly express that their method is a "promising tool for the selective manipulation and separation of cells, bacteria and other microorganisms, as well as viruses..." (page 431, 1st column, bottom paragraph).

Coupled with the artisans' explicit teaching which state that the integration of this module into a "lab-on-a-chip device" (page 431, 2nd column, 1st paragraph), one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success in combining the teachings of Burlage with the teachings of Pethig et al. and Lipshutz et al., so as to arrive at a method of selectively isolating and selecting cells from a heterogeneous population of cells, followed by the isolation of their nucleic acid molecules therein in an integrated device such as microfluidic device, for the purpose of determining/studying/identifying said nucleic acid molecules from the selectively isolated cells in a time efficient, reagent-efficient manner, with less contamination.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 70-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burlage (US 2003/0099928, published May 29, 2003, priority September 16, 1999) in view of Fu et al. (Nature Biotechnology, 1999, vol. 17, pages 1109-1111; IDS reference) and Lipshutz et al. (U.S. Patent No. 6,043,080, issued March 28, 2000).

Burlage discloses a method of separating particular cells from an environmental sample, wherein the method comprises:

a) providing an environmental sample comprising heterogeneous biological elements (section [0040]);

b) physically isolating an individual biological element or a subset of biological elements of the sample (sections [0010]; [0017]; [0035]; and [0065]);

c) lysing the isolated cells to liberate the nucleic acids present herein (section [0069]);

d) purification of the nucleic acids (section [0084]); and

e) amplification of the purified nucleic acid (sections [0069] and [0085]).

With regard to claim 71, the genetic diversity of a Pseudomonas is elucidated by sequence analysis (section [0088]).

With regard to claim 74, the artisan teaches that the genetic information represented by the amplified product is identified by sequencing and comparing against the known sequences (sections [0016]; [0072]; and [0088]).

With regard to claim 75, the artisans teaches that the isolated nucleic acid is cloned and cultured into a culturable microorganism to synthesize the gene product (section [0072]).

Burlage while conducting all of the steps of the claims, does not involve a microfluidic device, and particularly, the physical separation of cells is achieved by in situ hybridization followed by FACS (fluorescence-activated cell sorting; *see* sections [0059]; [0062]; and [0065]).

Fu et al. disclose a microfabricated fluorescence-activated cell sorter, which is capable of sorting individual cells, wherein the artisans explicitly state that microfabrication, "permits integration of cells sorting with other techniques such as PCR, microfabricated total analysis system, and DNA chip hybridization..." (page 1109, 2nd column, 1st paragraph).

Lipshutz et al. disclose a method of using a microfluidic device which comprises multiple chambers which conduct different types of assays, including sample preparation (column 2, lines 14-32), wherein the chambers include sample preparation chamber (column 4, lines 49-54; column 5, lines 15-20), which explicitly involve extraction of nucleic acids from the cells (column 5, lines 23-27), involving purification of the extracted nucleic acids from other components of the cells (column 5, lines 29-32), followed by the amplification of the nucleic acids (column 6, lines 25-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Burlage, Fu et al., and Lipshutz et al., thereby arriving at the claimed invention for the following reasons.

The motivation to analyze unculturable microorganisms from an environmental sample comprising a heterogeneous population of microorganisms is explicitly disclosed by Burlage:

> "Unculturable microorganisms are those microorganisms that cannot be grown in pure cultures by known means. It has been hypothesized that majority of microorganisms are unculturable in any microbial environment, for reasons that are unclear. These unculturable microorganisms represent a vast, untapped resources of DNA and of potential products such as enzymes and other protein products. These microorganisms undoubtedly have undiscovered enzymes that would be useful for environmental, medical, or industrial applications. However, these potential products are currently unavailable because there is no way to obtain pure DNA from such microorganisms. Microorganisms are presently studied at the genetic level by cloning and sequencing their DNA. However, this requires the

> cultivation of a large number of cells with subsequent extraction of the DNA from the batch. The same approach obviously can not be used for unculturable microorganisms." (sections [0003] and [0004]).

Based on such explicit motivation, one of ordinary skill in the art at the time the invention was made would have recognized the clear need to separate and individually analyze unculturable microorganisms from a sample comprising a heterogeneous population of microorganisms such as an environmental sample.

While Burlage employs techniques such as FACS for cell sorting, followed by subsequent manual operation of DNA extraction, and amplification of the extracted nucleic acids, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a microfluidic device which is well known and recognized in its ability to incorporate many biological assays into a single chip, so as to benefit from its ability to employ less sample/reagents, reduce the chances of contamination; and reduce the time required for the assay.

Fu et al. disclose a microfabricated FACS which is capable of sorting cells, wherein the artisans explicitly contemplate that microfabricatin permits integration of such units into other microfabricated systems (i.e., microfluidic device).

Given such an explicit motivational statement by Fu et al., one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success in combining the teachings of Burlage with the teachings of Fu et al. and Lipshutz et al., so as to arrive at a method of selectively isolating and selecting cells from a heterogeneous population of cells (via microfabricated FACS), followed by the isolation of their nucleic acid molecules therein in an integrated device such as microfluidic device, for the purpose of determining/studying/identifying said nucleic acid molecules from the selectively isolated cells in a time efficient, reagent-efficient manner, with less contamination.

One of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at combining the teachings of the artisans since Fu et al. conduct FACS assay for cell sorting, which is the same technique employed by Burlage, but on a microfabricated device. Since the integration of a microfabricated FACS is explicitly contemplated and envisioned by Fu et al., one of ordinary skill in the art would have also had a clear expectation of success at integrating the microfabricated FACS into any of the known microfluidic devices, such as that disclosed by Lipshutz et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
8/29/2006

YOUNG J. KIM
PRIMARY EXAMINER

YJK